DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

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APR 25 2000

Warning Letter

John A. Ferguson, M.D., CEO
Northeast Georgia Medical Center, Inc.
743 Spring Street, N.E.
Gainesville, Georgia 30501

Dear Dr. Ferguson:

From February 22 to March 1, 2000, Ms. Stephanie Hubbard, an investigator with the Food and Drug Administration (FDA), inspected the Northeast Georgia Medical Center, Inc. (NEGMC) Institutional Review Board (IRB). The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

We have received the IRB's letter dated March 31, 2000, in response to the observations listed on the Form FDA 483. Our comments on the IRB's response are provided below.

The inspection noted the following deficiencies:

1. **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a), 56.115(a)(6)]**

   A. There are no detailed instructions as to how the IRB is to operate.

   The IRB does not have an integrated document containing the IRB's detailed written procedures. Portions of the institutional Bylaws and sections from other policy and procedure manuals do not constitute adequate written procedures.

   The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures should describe the IRB organization, how many voting members make up the IRB, how IRB members are selected, explicitly outline how applications are processed, who will receive pre-meeting materials to review, how the review is to be conducted, how decisions are made, what criteria are used to determine the basis of approval of research proposals, the frequency of

continuing review, how continuing review is conducted, how controverted issues are decided, and describe how records must be maintained to fulfill federal requirements. The written procedures should define how the IRB will avoid conflict of interest in its reviews.

Written procedures should also address the following areas: expedited reviews, emergency use requests, how adverse reaction reports are reviewed, and the criteria for determining which projects require review more often than annually.

B. The procedures for conducting periodic review are not adequate.

Written procedures should describe in detail the following aspects of IRB continuing review operations: how and when renewal notices are sent to clinical investigators, how administrative staff processes interim reports, how periodic reports are discussed, the voting method the IRB will use for continuing reviews, and IRB follow-up activities in the event of a lack of response or an incomplete response. The procedures should specify how the IRB will document its actions for ensuring that progress reports are submitted and reviewed at the specified time intervals.

The content of progress reports should be described in detail so that clinical investigators will provide the IRB with interpretable periodic reports. For example, as a periodic report, Dr. [redacted] submitted a table of approximately 45 individual subjects enrolled in at least 13 different studies. There was no summary of adverse events, risks, or benefits for IRB consideration. These data are not readily interpretable by the IRB, and therefore do not provide a periodic report which is meaningful for the IRB's determination as to whether the studies should continue, be modified, or terminated. The IRB should require separate periodic reports for each study.

C. Written procedures should describe how the IRB will determine when an investigation involves a significant risk device.

D. Written procedures should describe in detail what record keeping practices will constitute adequate documentation of IRB activities.

E. The IRB should develop procedures for incorporating revisions to proposed research and for notifying the full IRB of those revisions. Written procedures should describe how the IRB will assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents.

F. There are no written procedures for ensuring prompt reporting to the appropriate institution officials and FDA of the following: (1) any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB; and, (3) any suspension or termination of IRB approval.

G. Procedures should describe in detail the sequence by which proposed research is reviewed by the IRB and other institutional committees, such as a Radiation Safety Committee. Will the IRB review a protocol if another committee review is pending? Does the IRB require documentation of approval from the chair of the other committees?

H. During the inspection, NEGMC staff stated that the institution is considering a [redacted] of the Bio-ethical Committee functions — [redacted] If [redacted] is implemented, the written procedures should explain how research proposals will be reviewed by [redacted], and whether one committee may override the decision [redacted]. We note that the IRB response letter describes that the institution is organizing a new Human Subject Protection Program.

I. Regarding the IRB membership, please define the role of the single non-voting member listed on the IRB membership roster. The role of guests should also be addressed if specific individuals regularly attend IRB meetings.

J. The procedure page titled "Elements required of Informed Consent for Research Studies" does not accurately state the requirement regarding confidentiality. Please identify the basic elements of informed consent as they are written in 21 CFR 50.25.

K. The IRB maintains a list of protocols approved by the IRB. Each project is associated with a designation such as "C [redacted]". The written procedures should explain the meaning of the letter and number designations so that the IRB may assign the designations in a consistent manner.

L. The IRB should consider requiring investigators to include the IRB approval date on consent forms to assure that the current consent form is used when the original consent form has been amended. This is not required by regulation, but it is considered to be a good practice.

We recognize that the IRB is in the process of developing a new IRB Policies and Procedures document to correct the deficiencies noted during the inspection. Please submit the IRB procedure document to this office when it has been approved by the institution.

2. **Failure to include at least one IRB member who is not otherwise affiliated with the institution. [21 CFR § 56.107(d)]**

   A. For an undetermined period in 1999, the IRB did not include a member who was not otherwise affiliated with the institution.

   B. We suggest that the IRB update the membership roster each time there is a change to reflect the actual membership. The IRB's practice of preparing a roster for a calendar year is not adequate to document that the membership requirements are met at any given time.

3. **Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, and include members with primary concerns in scientific and nonscientific areas. [21 CFR 56.108(c)]**

   A. The IRB reviewed and approved research when the requirement of a majority of voting members present was not met at 13 of the 14 meetings held during the period of February 1998 to February 2000. In several instances fewer than one-quarter of the members were present.

   B. The IRB approved research using telephone polling of IRB members. For example, during the meeting held March 16, 1999, the IRB allotted 10 minutes for the presentation of four new protocols. The IRB previously approved these studies "via phone call to quorum of members." Telephone polling is not an acceptable substitute for convened meetings.

4. **Failure to notify investigators in writing of its decision to approve or disapprove the proposed research. [21 CFR 56.109(e)]**

   The IRB does not consistently notify clinical investigators in writing of the IRB decision to approve or disapprove research, including continuing review. The Form FDA 483 identifies examples of studies for which this documentation is missing.

5. **Failure to conduct continuing review of research. [21 CFR 56.109(f)]**

   A. The IRB did not document the continuing review of three studies identified on the Form FDA 483. The clinical investigators were notified that the studies were approved, but there is no evidence that the studies were discussed by the IRB.

B. The IRB approved the continuation of at least one study even though the clinical investigator did not submit a periodic report.

C. The continuing review of one study was not conducted within the required time frame.

We recognize the IRB's promised correction of these deficiencies.

6. Failure to retain copies of all research proposals and supporting documents. [21 CFR § 56.115(a)(1)]

A. The IRB's practice of filing protocols, periodic reports, and other IRB correspondence attached to meeting minutes is inadequate. This system does not allow the IRB to readily determine the status of a study or to locate all the documents associated with a specific protocol. There is no log or listing of ongoing studies and no way to quickly determine the status of an ongoing study.

B. The IRB does not maintain copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved consent forms, progress reports submitted by clinical investigators, and reports of adverse events to subjects. The Form FDA 483 lists several examples of documents that could not be retrieved from the IRB's files.

C. There is no documentation of the manner in which the periodic review of research is conducted.

We recognize the IRB commitment to develop a document management system to maintain these records.

7. Failure to prepare detailed meeting minutes. [21 CFR § 56.115(a)(2)]

A. Minutes of IRB meetings should include the numbers of members who voted for, against, or abstained from voting on actions before the IRB. This information is important to document whether the IRB decision is unanimous, and whether IRB members or alternates exclude themselves from deliberation and voting on their own research projects and on projects for which they have a conflict of interest.

B. Meeting minutes do not consistently document the details of recommended changes to protocols and consent forms. The minutes should include the basis for requiring changes in or disapproving research proposals, and a summary of the discussion of controverted issues and their resolution.

The minutes often state that the IRB discussed concerns about some aspect of the study, but the specific concerns are not documented. For example, the meeting minutes document that IRB concluded that a study consent form should be revised quickly to include additional potential risks to the subjects, but the details of the risks and desired changes are omitted.

C. Meeting minutes do not identify which periodic reports have been received since the previous meeting.

D. Meeting minutes do not consistently record that previously requested protocol changes and/or clarifications have been received by the IRB.

E. Meeting minutes do not always identify the identification/tracking number of the study which was discussed and voted on during a meeting. In many cases a protocol number is included in the meeting minutes, but the practice is not routine. The meeting minutes should identify each study for which continuing review was conducted.

F. The IRB meeting minutes of December 5, 1997, do not document that the IRB determined whether an investigational device is a significant risk device or a non-significant risk device.

G. The meeting minutes do not consistently identify the non-members who are present during IRB meetings. Designations could include terms like "guest" or "observer."

The IRB's response letter states the commitment to develop procedures and fulfill the requirements for documenting the IRB's review of research.

We acknowledge that the IRB promised to implement corrective actions within targeted time frames. We also recognize that the IRB voluntarily restricted its activities until it has implemented some of the corrective actions. The reintroduction of previously approved studies through the reorganized IRB appears to be an appropriate approach given that the IRB is being reorganized.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the status of the proposed actions you have initiated to bring the procedures of the IRB into compliance with FDA requirements.

Failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include, but are not limited to, the termination of all ongoing studies approved by your IRB, and the initiation of regulatory proceedings for IRB disqualification.

Your file will remain open until we receive your response and the IRB's revised procedures, and they are deemed adequate. You may find it helpful to refer to the *FDA Information Sheets on FDA's* web site (http://www.fda.gov/oc/oha/IRB/toc.html). Appendix H provides a guide to ensure that all required elements are included in your written procedures.

If you have questions or comments about the contents of this letter or any aspects of the operation and responsibilities of an Institutional Review Board, you may contact Patricia Holobaugh, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301) 827-6347.

Your written response should be addressed to:

Ms. Patricia Holobaugh (HFM-650)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone: (301) 827-6347

Sincerely,

Steven A. Masiello
Director
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Center for Biologics Evaluation
and Research

cc: Henry C. Rigdon, COO
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Everett Roseberry, M.D., Chair
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cc: H.Q. Classification: OAI

HFM-1	
HFM-600	
HFM-650	
HFM-650	Holobaugh
HFM-650	ACCESS/Chron
HFM-650	warning letter file
HFM-610	
HFC-132	
HFC-230	
HFD-47	
HFZ-310	
HFA-224	
HFM-48	purge before distribution to HFI-35 *with attached coversheet for web posting*
HFR-SE100	Director
HFR-SE150	BIMO Coordinator
HFR-SE150	Hubbard

final:Holobaugh:4-7-00 NE_GeorgiaMC_IRB.let.wpd
revised:response received:4-12-00
final:Holobaugh:4-13-00